A Phase III Study of BBI-608 in combination with 5-Fluorouracil, Leucovorin, Irinotecan (FOLFIRI) in Adult Patients with Previously Treated Metastatic Colorectal Cancer (CRC)

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Primary objective of the study:* To compare overall survival (OS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2)* To compare OS in the pSTAT3-positive (pSTAT3(+)) Subpopulation...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55360

Source
ToetsingOnline

Brief title
CanStem303C

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
bowel cancer, Colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Boston Biomedical, Inc
Source(s) of monetary or material Support: Boston Biomedical;Inc.

Intervention

Keyword: Adult Patients, BBI-608, FOLFIRI, Metastatic Colorectal Cancer

Outcome measures

Primary outcome

Primary Endpoint for the Study:

* Overall Survival in the General Population and pSTAT3(+) Subpopulation

Secondary outcome

Key Secondary Endpoints for the Study:

* Progression-Free Survival in the General Population and the pSTAT3(+)

Subpopulation

* Disease Control Rate in the General Population and the pSTAT3(+) Subpopulation

* Objective Response Rate in the General Population and the pSTAT3(+)

Subpopulation

Other Secondary Endpoints for the Study:

* Quality of Life Analysis in the General Population and the pSTAT3(+)

Subpopulation

* Safety Analysis

Study description

Background summary

BBI-608 is a product candidate designed by Boston Biomedical, Inc. (BBI) to target CSCs. BBI-608 is a small molecule that blocks self-renewal of, and induces cell death in, CSCs isolated from CRC and other types of cancer. BBI-608 inhibits CSCs by binding to CSCP3, a proprietary CSC target discovered by scientists at Boston Biomedical. CSCP3 has been identified as STAT3. STAT3 is a known oncogene which is aberrantly activated in a wide variety of human cancers including all the major carcinomas as well as some hematologic tumors. In particular, nearly 200 peer-reviewed scientific articles have established dysregulation of STAT3 signaling as a key feature of human CRC. Moreover, elevated expression of phosphorylated STAT3 by immunohistochemistry from archival patient tumor samples has been associated with poor prognosis [Morikawa 2011].

When administered in mouse xenograft models, chemotherapeutic agents, including 5-FU and irinotecan increase pSTAT3 levels and enrich cancer stem cells abundance. BBI-608 is able to significantly decrease pSTAT3 levels as well as deplete stem cell abundance, and blocks the induction of pSTAT3 and cancer stem cells by these chemotherapeutic agents. Similar encouraging preclinical data is seen when BBI-608 is combined with either oxaliplatin, or regorafenib. In vitro, treatment with BBI-608 combined with irinotecan or 5-FU results in potent and synergistic colony formation inhibition in multiple CRC cell lines. Additionally, combined treatment with BBI-608 and irinotecan or 5-FU suppresses levels of p-STAT3 and *-catenin, while monotherapy with irinotecan or 5-FU leads to upregulation of these proteins. Tumor tissue of combination-treated animals reveals synergy with increase in cancer cell death and decrease in tumor cell proliferation.

These data provide strong rationale for the development of BBI-608 in combination with 5-FU and irinotecan for CRC therapies based on inhibition of STAT3 activity.

Study objective

Primary objective of the study:
* To compare overall survival (OS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2)
* To compare OS in the pSTAT3-positive (pSTAT3(+)) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2)

Key secondary objectives of the study:
* To compare progression free survival (PFS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI
* To compare PFS in the pSTAT3(+) Subpopulation patients treated with BBI 608 plus biweekly FOLFIRI versus biweekly FOLFIRI
* To compare disease control rate (DCR) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI

* To compare DCR in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI
* To compare overall response rate (ORR) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI
* To compare ORR in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI
Other Secondary Objectives:
* To compare the Quality of Life (QoL), as measured using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30), in the General Population patients treated with BBI-608 plus bi-weekly FOLFIRI versus bi-weekly FOLFIRI
* To compare the QoL, as measured using the EORTC-QLQ-C30, in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI
* To evaluate the safety profile of BBI-608 administered daily plus biweekly FOLFIRI with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0 in the General Population and the pSTAT3(+) Subpopulation

Study design

This is an international multi-center, prospective, open-label, randomized, adaptive design Phase 3 trial of the cancer stem cell pathway inhibitor BBI-608 plus standard bi-weekly FOLFIRI (Arm 1) versus standard bi-weekly FOLFIRI (Arm 2) in patients with previously treated metastatic colorectal cancer (mCRC). The hypotheses in General Population and pSTAT3(+) Subpopulation for OS in the study will be tested. An interim analysis will be conducted to check the decision rules of futility, population and hypothesis selection, and event count adjustment. The Sponsor and the CRO have implement blinding plans to minimize bias prior to the interim and final analyses.

In this study, adult patients with mCRC following progression on first-line FOLFOX or XELOX with or without bevacizumab will be randomized in a 1:1 ratio to BBI-608 plus biweekly FOLFIRI (Arm 1) or biweekly FOLFIRI (Arm 2). Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible. Patients will be stratified according to geographical region (North America/Western Europe/Australia, vs. Japan/Korea vs. rest of the world); time to progression from start of first line therapy (<6 months vs. *6 months); RAS mutation status (mutant vs. wild type), bevacizumab as part of their protocol treatment (yes vs. no), and location of the primary tumor (left vs. right colon).

The study will proceed in 14-day (2-week) cycles. BBI-608 will be administered orally, twice daily, with doses separated by approximately 12 hours. Standard FOLFIRI will be administered biweekly, on Day 1 of each 14-day study cycle. BBI-608 administration will begin 2 to 5 days prior to the first FOLFIRI infusion in patients randomized to Arm 1. In Investigator selected patients,

bevacizumab will be administered per product label and institutional standards.

Tumor assessments will be performed every 8 weeks after randomization until 6 months of treatment and every 12 weeks thereafter until objective disease progression.

Retrospective analysis of archival tumor tissue samples will be performed at the time of the interim analysis to determine pSTAT3 status of randomized patients.

Intervention

Patients will be randomized according to a 1:1 ratio using a permuted block randomization procedure to receive one of the following treatments: BBI-608 plus standard bi-weekly FOLFIRI or standard bi-weekly FOLFIRI to a planned sample size of 1250 subjects. Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice,will be permissible.

Patients will be randomized to one of the following two arms:
Arm Agent(s) Dose and Route Duration
1 BBI-608 240 mg orally two times daily
FOLFIRI Standard FOLFIRI IV, once every 2 weeks
2 FOLFIRI Standard FOLFIRI IV, once every 2 weeks

Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST1.1 criteria.

Study burden and risks

Please refer to section E9.

Contacts

Public
Boston Biomedical, Inc

Memorial Drive 640
Cambridge MA 02139
US
Scientific
Boston Biomedical, Inc

Memorial Drive 640
Cambridge MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.1 Written, signed consent for trial participation must be obtained from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study specific procedure., 1.2 Must have histologically confirmed advanced CRC that is metastatic., 1.3 Must have failed treatment with one regimen containing only a fluoropyrimidine and oxaliplatin with or without bevacizumab for metastatic disease. All patients must have received a minimum of 6 weeks of the first-line regimen that included bevacizumab, oxaliplatin and a fluoropyrimidine with or without bevacizumab in the same cycle. Treatment failure is defined as radiologic progression during or < 6 months after the last dose of first-line therapy., 1.4 FOLFIRI therapy is appropriate for the patient and is recommended by the Investigator., 1.5 Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease performed within 21 days prior to randomization. Patients with either measurable disease or non-measurable evaluable disease are eligible., 1.6 Must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1., 1.7 Must be * 18 years of age., 1.8 For male or female patient of child bearing potential: Must agree to use contraception or take measures to avoid pregnancy during the study and for 180 days for female and for male patients, of the final FOLFIRI dose. Patients who receive single agent BBI-608 without FOLFIRI must agree to use contraception or take measures to avoid pregnancy during the study and for 30 days for female patients and 90 days for male patients, of the final BBI-608 dose. , 1.9 Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 5 days prior

to randomization. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG., 1.10 Must have alanine transaminase (ALT) * 3 × institutional upper limit of normal (ULN) [* 5 × ULN in presence of liver metastases] within 14 days prior to randomization., 1.11 Must have hemoglobin (Hgb) * 9.0 g/dL within 14 days prior to randomization. Must not have required transfusion of red blood cells within 1 week of baseline Hgb assessment., 1.12 Must have total bilirubin * 1.5 × institutional ULN [* 2.0 x ULN in presence of liver metastases] within 14 days prior to randomization., 1.13 Must have creatinine * 1.5 × institutional ULN or Creatinine Clearance > 50 ml/min as calculated by the Cockcroft-Gault equation (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation may also be used) within 14 days prior to randomization., 1.14 Must have absolute neutrophil count * 1.5 x 109/L within 14 days prior to randomization., 1.15 Must have platelet count * 100 x 109/L within 14 days prior to randomization. Must not have required transfusion of platelets within 1 week of baseline platelet assessment., 1.16 Patient must have adequate nutritional status with Body Mass Index (BMI) > 18 kg/m2 and body weight of > 40 kg with serum albumin > 3 g/dL., 1.17 Other baseline laboratory evaluations, listed in Section 5, must be done within 14 days prior to randomization., 1.18 Patient must consent to provision of, and Investigator(s) must confirm access to and agree to submit a representative formalin fixed paraffin block of tumor tissue in order that the specific biomarker assays proscribed may be conducted (Section 12.2.1. and Section 13.2)., 1.19 Patient must consent to provision of a sample of blood in order that the specific correlative marker assays may be conducted (Section 12.2.1)., 1.20 Patients must be accessible for treatment and follow-up., 1.21 Protocol treatment is to begin within 2 calendar days of patient randomization for patients randomized to Arm 1. Patients randomized to Arm 2 must begin protocol treatment within 7 calendar days of randomization., 1.22 The patient is not receiving therapy in a concurrent clinical study and the patient agrees not to participate in other interventional clinical studies during their participation in this trial while on study treatment. , (Please refer to protocol for further information)

Exclusion criteria

2.1 Anti-cancer chemotherapy or biologic therapy if administered prior to the first planned dose of study medication (BBI-608 or FOLFIRI) within period of time equivalent to the usual cycle length of the regimen. An exception is made for oral fluoropyrimidines (e.g. capecitabine, S-1), where a minimum of 10 days since last dose must be observed prior to the first planned dose of study medication., 2.2 More than one prior chemotherapy regimen administered in the metastatic setting., 2.3 Major surgery within 4 weeks prior to randomization., 2.4 Patients with any known brain or leptomeningeal metastases are excluded, even if treated., 2.5 Women who are pregnant or breastfeeding. Women should not breastfeed while taking study treatment and for 4 weeks after the last dose of BBI-608 or while undergoing treatment with FOLFIRI and for 180 days after the

last dose of FOLFIRI., 2.6 Gastrointestinal disorder(s) which, in the opinion of the Qualified/Principal Investigator, would significantly impede the absorption of an oral agent (e.g. active Crohn*s disease, ulcerative colitis, extensive gastric and small intestine resection)., 2.7 Unable or unwilling to swallow BBI-608 capsules daily., 2.8 Prior treatment with BBI-608 or possible hypersensitivity to BBI-608 or one of the excipients which include azo dyes sunset yellow and allura red., 2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements.
a. Known infection with HIV, and/or active infection with hep B or hep C
b. patients with clinically significant ascites or pleural effusions, 2.10 Known hypersensitivity to 5-fluorouracil/leucovorin, 2.11 Known dihydropyrimidine dehydrogenase (DPD) deficiency, 2.12 Known hypersensitivity to irinotecan, 2.13 Abnormal glucuronidation of bilirubin, known Gilbert*s syndrome, 2.14 Patients with QTc interval > 470 milliseconds, 2.15 For patients to be treated with a regimen containing bevacizumab: please refer to protocol, 2.16 Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated with no evidence of disease for > 3 years., 2.17 Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy., 2.18 Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol., Please refer to protocol for further information.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2017
Enrollment:	49
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BBI608
Generic name:	napabucasin
Product type:	Medicine
Brand name:	Benda-5 FU 50 mg/ml solution for injection
Generic name:	5-Fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Bendafolin 10mg/ml, solution for injection
Generic name:	Folinic Acid/Leucovorine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Irinotecan Bendalis 20mg/mll, concentrate for solution of infusion
Generic name:	Irinotecan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-09-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-11-2016
Application type:	First submission

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-03-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-02-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-05-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-11-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2021
Application type:	Amendment

Review commission: METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-001627-31-NL
ClinicalTrials.gov	NCT02753127
CCMO	NL58412.028.16